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(54) Title: TOPICAL POLYMERIC DRUG DELIVERY SYSTEM

(57) Abstract

A topical polymeric drug delivery system for the delivery of drugs to the skin for either topical or systemic effect is described. The system involves the use of a propellant-free airless pump for the delivery.

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TITLE OF THE INVENTION

TOPICAL POLYMERIC DRUG DELIVERY SYSTEM

This application is a continuation-in-part of copending application Serial No. 08/238,409 filed May 5, 1994.

BACKGROUND OF THE INVENTION

The present invention is directed to a topical polymeric delivery system for the administration of certain drugs over an extended period of time via a non-propellant aerosol pump device.

Sustained release devices for controlled topical delivery of drugs is a highly useful method of supplying medication when it is beneficial to administer medication continuously. The idea of aerosol delivery of a thin film for direct spraying on a wound has been described in an article by Fujita et al., "Pharmaceutical Research" 9, (1992). However, the method described involves a CFC containing aerosol propellant.

Some of the advantages of this system over known transdermal delivery systems include:

1) Ease of application;
2) Ease of removal since the film is water soluble;
3) Freedom from adhesives;
4) Freedom from the use of a rate controlling membrane;
5) High patient acceptability as the film is practically invisible; and
6) The use of a propellant-free aerosol which is environmentally friendly.

SUMMARY OF THE INVENTION

According to the present invention it has been discovered that certain drugs can be delivered via a propellant-free aerosol as a component of a polymeric system for prolonged administration compared to conventional formulations. In particular, the compound indomethacin and certain cyclooxygenase II inhibitors such as 3-[3,4-

difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone can be topically applied using the delivery system of the invention resulting in prolonged administration compared to conventional dosage forms. Furthermore, the system is capable of providing systemic delivery of the medicament without causing the gastric irritation associated with indomethacin, in particular, and NSAIDs, in general.

DESCRIPTION OF THE INVENTION

There has been discovered a novel polymeric drug delivery system for prolonged topical delivery of a medicament via a propellant-free aerosol pump. The system is adaptable to any drug which is soluble and stable in hydroalcoholic solutions and comprises a film forming polymer, a plasticizing agent, a crystallization inhibitor/stabilizer, a penetration enhancer, an alcoholic or hydroalcoholic solution and a suitable drug .

Suitable drugs for use in therapy with the device of the invention include without limitation:

1. Protein drugs such as insulin;
2. Anti-infectives, such as antibiotics, including penicillin, tetracycline, chlorotetracycline bacitracin, nystatin, streptomycin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides, including sulfacetamide, sulfamethizole, sulfamethazine, sulfadiazine, sulfamerazine, and sulfisoxazole, cefoxitin; anti-virals including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate;
3. Steroidal anti-inflammatory agents such as hydrocortisone, cortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-phosphate and prednisolone acetate;
4. Estrogens such as estrone, 17 β-estradiol, ethinyl estradiol and diethyl stilbesterol;

5. Progestational agents such as progesterone, megestrol, melengestrol, chlormadinone, ethisterone, norethynodrel, 19-nor-progesterone, norethindrone, medroxyprogesterone and 17 β-hydroxy-progesterone;
6. Humoral agents such as the prostaglandins, for example, PGE_1, PGE_2 and PFG_2;
7. Antipyretics analgesics such as aspirin, sodium salicylate, salicylamide and diflunisal;
8. Antispasmodics such as atropine, methantheline, papaverine and methscopolamine bromide;
9. Antihistamines such as diphenhydramine, dimenhydrinate, tripelennamine, perphenazine and chlorophenazine;
10. Non steroidal anti-inflammatory agents such as indomethacin and sulindac; and
11. Cyclooxygenase II inhibitors such as those disclosed in U.S. Patent No. 5,409,944 issued April 25, 1995 and those disclosed in copending applications 08/147,804 filed November 4, 1993; 08/179,467 filed January 10, 1994; 08/330,172 filed October 27, 1994; 08/361,268 filed December 21, 1994 and 08/371,179 filed January 11, 1995.

Other drugs having the same or different physiological activity as those recited above can be employed in drug-delivery devices within the scope of the present invention.

This system is particularly useful with drugs such as indomethacin which can cause severe upper gastrointestinal irritation and nausea when administered by conventional means.

The system involves the use of film forming polymers which are soluble and rapidly form a thin film upon application via a hydrocarbon propellant-free system. The film formed allows vapor penetration and can be considered breathable. The choice of a chloro-fluoro-carbon (CFC) free preparation was essential due to the potentially environmentally damaging characteristics of CFC propellants. With the use of a hydrocarbon propellant-free system, it was also essential that the solvent employed be volatile enough to allow

rapid film formation on administration. Alcohols or hydroalcoholic solutions using lower alkanol solvents such as ethanol and isopropanol have been found useful with ethanol being the preferred solvent. Other potential solvent systems may include ethyl acetate.

The film forming polymer selected was determined in view of the solvent employed. It is necessary that the polymer be soluble in the solvent chosen. Polymers which have been found to be useful in the invention include methacrylates, celluloses, siloxanes and copolymers of methacrylates, celluloses and siloxanes. Preferred polymers are methacrylates with poly(2-hydroxy ethyl methacrylate) (PHEMA) the most preferred choice. PHEMA was the most preferred because of the quality of the film formed in the system.

Plasticizing agents are also necessary for the delivery system. The plasticizers are used to impart the desired mechanical properties to the film such as flexibility. Suitable plasticizing agents include Tween 20 (polyoxyethylene (20) sorbitan monolaurate) and Tweens of higher molecular weight, low molecular weight polyethylene glycols, glycerine or Labrasols (PEG-8-caprylic-capritriglyceride). Preferred plasticizers are Tweens with Tween 20 the most preferred. The plasticizing agent is generally present in an amount from about 10% - 50% as a percentage of the total solid contents of the film.

An additional component for the delivery system is a crystallization inhibitor/stabilizer and/or a penetration enhancer. These are used to modulate drug delivery. Suitable compounds include substituted cyclodextrins such as hydroxylpropyl beta-cyclodextrin (HPBCD), hydroxyethyl beta-cyclodextrin, diethyl beta-cyclodextrin and hydroxyethyl and hydroxypropyl gamma cyclodextrin and transcutol, urea and isoterpenes. The choice of cyclodextrin is governed by the size of the drug molecule used in the particular formulation. Hydroxypropyl beta-cyclodextrin (HPBCD) was the preferred crystallization inhibitor.

The following example illustrates the invention but is not construed to be limiting.

EXAMPLE I

Film Formation

PHEMA was dissolved in a Tween/ethanol solution which had been warmed to 50°C. Indomethacin free acid was added to the solution and when fully dissolved the resultant solution was poured into a glass petri dish. The petri dish was covered with an inverted funnel and the solution was left to evaporate to dryness at room temperature. The films were placed in a vacuum oven for 16 hours at 37°C to ensure that the moisture level in all films was comparable. Moisture levels were determined to be less than 3%, in all films, by thermogravimetric analysis. As a percentage of the total solid contents of the film, indomethacin was present in quantities ranging from 9 to 14%, and Tween 20 from 14 to 45%. In films containing HPBCD, quantities were used which gave molar ratios of 1:1, 1:2 and 1:3, indomethacin:HPBCD.

EXAMPLE II

In Vitro Dissolution Testing of Films with Indomethacin

Films were cut to the appropriate size to fit an Enhancer cell (Vankel Industries, USA) and were weighed before testing. The film was covered with a Durapore membrane filter (Millipore, USA) to provide additional mechanical support. Dissolution testing, using the USP paddle method (100 r.p.m.), was carried out in phosphate buffer (pH 7.2) at 37°C. Samples were taken over an eight hour period and indomethacin concentration was quantitated by HPLC.

HPLC Conditions

A Beckman Ultrasphere 5µ C-18 (4.6 x 250 mm) column was used at 40°C with a mobile phase of 35% aqueous (3% acetic acid in distilled water) and 65% organic (15% acetonitrile and 85% methanol) phases. Flow rate was 1 ml/min. When analyzing Indomethacin

samples and standards, 4-androsten-17β-ol-3-one (testosterone) was used as an internal standard. Detection was by UV spectroscopy measuring at 260 nm. An indomethacin standard curve was constructed by preparing standards in methanol which ranged from 0.5 to 10 µg/ml each with 10 µg/ml of testosterone. The limit of detection for indomethacin quantitation by HPLC with UV detection at 260 nm was determined as 0.05 µg/ml. Determination was linear over the range 0.1 to 100 µg/ml. The uniformity of detection was determined by injecting the same standard ten times and determining the relative standard deviation for the peak areas obtained. The relative standard deviation was less than two.

EXAMPLE III

Film Formation

PHEMA was dissolved in a Tween/HPBCD/ethanol solution which had been warmed to 50°C. 3-[3,4-Difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone was added to the solution and stirred until fully dissolved. The resulting solution was filled into a Valois airless pump and made up to volume with ethanol. The pump was sealed with a metered valve (200ml, VP36, 20mm CS gasket 3/522,spring 1674). As a percentage of the total solid content of the film 3-[3,4-difluoro-phenyl]- 4-[4-(methylsulfonyl) phenyl] -2 (5H)-furanone was present in quantities ranging from 1.15% to 4.45%, HPBCD at 10% and Tween 20 from 14 to 45%.

Rat Paw Edema Assay-Protocol

Five Fuzzy rats (250-300g) (Harlan Sprague Dawley, Indianapolis, IN.USA) were used. The dorsal mid-lumbar area was sprayed topically with the formulation covering an area of about 4 x 4 cm. This administration was given once a day for three days. On the third day, one hour after the topical administration, a line was drawn using a permanent marker at the level above the ankle in one hind paw

to define the area of the paw to be monitored. The paw volume was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected subplantarly with 50 µl of a 1% carrageenan solution in saline (FMC Corp., Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e., 500 µg carrageenan per paw). Three hours later, the paw volume was measured and the increases in the paw volume were calculated. A five hour plasma sample was also taken to correlate the plasma levels with % paw edema inhibition. The animals were euthanized by $C0_2$ asphyxiation. Paw edema data were compared with the vehicle control group and percent inhibition calculated taking the values in the control group as 100%. The topical formulation was given at different doses to the animals and was also compared to an orally administered dose of indomethacin and a commercially available topical gel formulation of indomethacin. Representative results are shown in Table 1.

Table 1

Formulations	Dose(mg/kg)	% Inhibition (3hr)	Plasma Conc (μg/ml) (5hr)
Indomethacin spray	1	31 ± 1	3.6 ± 1.2
	3	54 ± 2	7.6 ± 2.1
	10	70 ± 2	8.5 ± 1.2
Amuno® Gel	5	41 ± 2	4.5 ± 1.5
Oral Indomethacin (0.5% Methocel)	3	55 ±3	7.2 ± 3.1
3-[3,4-Difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone spray	7	56 ± 5	1.2 ± 0.2

WHAT IS CLAIMED IS:

1. A topical polymeric delivery system suitable for administering a drug soluble in hydroalcoholic solutions which comprises:

(a) a film forming polymer;
(b) a plasticizing agent;
(c) a crystallization inhibitor/stabilizer;
(d) a penetration enhancer;
(e) an alcoholic or hydroalcoholic solution; and
(f) a suitable drug.

2. The system according to Claim 1 wherein the drug is optionally administered via a propellant-free aerosol pump.

3. The system according to Claim 1 wherein the film forming polymer is selected from the group consisting of methacrylates, celluloses and siloxanes and co-polymers of methacrylates, celluloses and siloxanes.

4. The system according to Claim 3 wherein the film forming polymer is a methacrylate.

5. The system according to Claim 4 wherein the methacrylate is poly(2-hydroxy ethyl methacrylate).

6. The system according to Claim 1 wherein the plasticizing agent is selected from Tween, low molecular weight polyglycols, glycerin or Labrasols.

7. The system according to Claim 6 wherein the plasticizing agent is Tween 20.

8. The system according to Claim 1 wherein the crystallization inhibitor is selected from the group consisting of hydroxypropyl beta-cyclodextrin, hydroxyethyl beta-cyclodextrin, diethyl beta-cyclodextrin, hydroxyethyl gamma-cyclodextrin or hydroxypropyl gamma-cyclodextrin.

9. The system according to Claim 1 wherein the suitable drug is selected from the group consisting of

a) Protein drugs such as insulin;

b) Anti-infectives, such as antibiotics, including penicillin, tetracycline, chlorotetracycline bacitracin, nystatin, streptomycin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides, including sulfacetamide, sulfamethizole, sulfamethazine, sulfadiazine, sulfamerazine, and sulfisoxazole, cefoxitin; anti-virals including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate;

c) Steroidal anti-inflammatory agents such as hydrocortisone, cortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-phosphate, and prednisolone acetate;

d) Estrogens such as estrone, 17 β-estradiol, ethinyl estradiol, and diethyl stilbesterol;

e) Progestational agents such as progesterone, megestrol, melengestrol, chlormadinone, ethisterone, norethynodrel, 19-nor-progesterone, norethindrone, medroxyprogesterone and 17 β-hydroxy-progesterone;

f) Humoral agents such as the prostaglandins, for example, PGE_1, PGE_2 and PFG_2;

g) Antipyretics analgesics such as aspirin, sodium salicylate, salicylamide, and diflunisal;

h) Antispasmodics such as atropine, methantheline, papaverine, and methscopolamine bromide;

i) Antihistamines such as diphenhydramine, dimenhydrinate, tripelennamine, perphenazine, and chlorophenazine;

j) Non steroidal anti-inflammatory agents such as indomethacin, and sulindac; and

k) Cyclooxygenase II inhibitors such as 3-[3,4-difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone.

10. The system according to Claim 9 wherein the drug is selected from the group consisting of non-steroidal and steroidal anti-inflammatory agents, antihistamines and cyclooxygenase II inhibitors.

11. A method for the topical or systemic delivery of a therapeutic dose of a drug selected from the group consisting of

a) Protein drugs such as insulin;

b) Anti-infectives, such as antibiotics, including penicillin, tetracycline, chlorotetracycline bacitracin, nystatin, streptomycin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides, including sulfacetamide, sulfamethizole, sulfamethazine, sulfadiazine, sulfamerazine, and sulfisoxazole, cefoxitin; anti-virals including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate;

c) Steroidal anti-inflammatory agents such as hydrocortisone, cortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-phosphate, and prednisolone acetate;

d) Estrogens such as estrone, 17 β-estradiol, ethinyl estradiol, and diethyl stilbesterol;

e) Progestational agents such as progesterone, megestrol, melengestrol, chlormadinone, ethisterone, norethynodrel, 19-nor-progesterone, norethindrone, medroxyprogesterone and 17 β-hydroxy-progesterone;

f) Humoral agents such as the prostaglandins, for example, PGE_1, PGE_2 and PFG_2;

g) Antipyretics analgesics such as aspirin, sodium salicylate, salicylamide and diflunisal;

h) Antispasmodics such as atropine, methantheline, papaverine and methscopolamine bromide;

i) Antihistamines such as diphenhydramine, dimenhydrinate, tripelennamine, perphenazine and chlorophenazine;

j) Non steroidal anti-inflammatory agents such as indomethacin and sulindac

k) Cyclooxygenase II inhibitors such as 3-[3,4-difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone

which comprises employing the system of Claim 1.

12. A method for the topical or systemic delivery of a therapeutic dose of a drug selected from the group consisting of non-steroidal and steroidal anti-inflammatory agents, antihistamines and cyclooxygenase II inhibitors which comprises employing the system of Claim 1.

13 A method for the topical or systemic delivery of a therapeutic dose of indomethacin which comprises employing the system of Claim 1.

14. A topical polymeric delivery system according to Claim 1 wherein the polymer is poly(2-hydroxy ethyl methacrylate), the plasticizing agent is Tween 20, the crystallization inhibitor is

hydroxypropyl beta-cyclodextrin, the alcoholic solution is absolute ethanol and the drug is indomethacin.

15. A method for the topical or systemic delivery of a therapeutic dose of 3-[3,4-difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone which comprises employing the system of Claim 1.

16. A topical polymeric delivery system according to Claim 1 wherein the polymer is poly(2-hydroxy ethyl methacrylate), the plasticizing agent is Tween 20, the crystallization inhibitor is hydroxypropyl beta-cyclodextrin, the alcoholic solution is absolute ethanol and the drug is 3-[3,4-difluorophenyl]-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone.

17. A topical polymeric delivery system for administering a drug which comprises:

(a) a film forming polymer;
(b) a plasticizing agent;
(c) a solvent effective for film formation of said polymer, and
(d) at least one of:
    (i) a crystallization inhibitor/stabilizer; and
    (ii) a penetration enhancer.

18. A system of Claim 18 for use in topical or systemic delivery of a drug soluble in said solvent.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/CA 95/00260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 997 643 (UNION CARBIDE CHEMICALS AND PLASTICS COMPANY INC.) 5 March 1991 see column 4-5; claims 1,2,9 see column 8, line 1-40 ---	1-6,9, 11,17,18
X	US,A,5 158 766 (ECOLAB INC.) 27 October 1992 see column 4; claims 1,6,8,10,12 see column 7 ---	2-6,9, 11,17,18
X	EP,A,0 408 069 (UNION CARBIDE CHEMICALS AND PLASTICS COMPANY INC.) 16 January 1991 see page 3-4; claims 1,5-7,9-11 see page 8-10 --- -/--	1,2,6, 9-13,17, 18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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National Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	see page 3-4; claims 1,7,8	1-4,6, 9-14
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